

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: PAMELA J. SHERWOOD
BOZICEVIC, FIELD & FRANCIS LLP
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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference STAN-177WO	Date of Mailing (day/month/year) 29 AUG 2001
International application No. PCT/US01/15385	International filing date (day/month/year) 11 MAY 2001
Applicant THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer FOZIA HAMUD Telephone No. (703) 308-0196
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WAP
PJS

DOCKETED 9/6
article 19 due 10/29/01
suppl. IDS was 11/29/01

[Signature]

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference STAN-177WO	<div style="display: flex; justify-content: space-between;"> <div> FOR FURTHER ACTION </div> <div> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. </div> </div>
International application No. PCT/US01/15385	<div style="display: flex; justify-content: space-between;"> <div> International filing date (day/month/year) 11 MAY 2001 </div> <div> (Earliest) Priority Date (day/month/year) 11 MAY 2000 </div> </div>
Applicant THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY	

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:
 - ☒ contained in the international application in written form.
 - ☒ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☐ furnished subsequently to this Authority in computer readable form.
 - ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the
 - ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
- 2. ☐ Certain claims were found unsearchable (See Box I).
- 3. ☒ Unity of invention is lacking (See Box II).
- 4. With regard to the **title**,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established by this Authority to read as follows:
- 5. With regard to the **abstract**,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
- 6. The figure of the **drawings** to be published with the abstract is Figure No. ____
 - ☐ as suggested by the applicant.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/15385**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-13, SEQ ID NOs:5-8

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/15385

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/12, 5/10; C12P 21/02; C07K 14/47

US CL : 435/69.1, 71.1, 320.1, 471, 252.3; 536/23.5; 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/69.1, 71.1, 320.1, 471, 252.3; 536/23.5; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

West US Patent full, STN via medline, caplus, embase. SEQ ID NOs:5-8, search terms: GRAIL protein or polypeptide or peptide; anergy; immune or antigen or antibody

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	Database GenBank (EST); Accession NO: AI987883; MARRA et al. mouse clone; 02 September 1999; having at least 18 and 50 contiguous nucleotides of SEQ ID NO:5. See sequence comparison "A" of instant SEQ ID NO:5 and reference sequence.	3-6 ----- 7-10
Y	Database SPTREMBL; Accession NO: 076671; 01 November 1998; WILSON et al. H10E21.5 Protein; having a fragment of at least 12 amino acids of SEQ ID NO:6; see sequence comparison "B"	13
X	ROEP, B.O. Perspectives in Diabetes - T-Cell Responses to Autoantigens in IDDM: The Search for the Holly Grail. Diabetes. September 1996, Vol. 45, No. 9, pages 1147-1156, see especially table 1 on page 1148 and page 1150, column 2.	1

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"A"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 23 JULY 2001	Date of mailing of the international search report 29 AUG 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer FOZIA HAMUD Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/15385

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MCLACHLAN et al. Editorial: Monoclonal, Human Autoantibodies to the TSH Receptor-The Holly Grail and Why Are We looking for It. Journal of Clinical Endocrinology and Metabolism. September 1996, Vol. 81, No. 9, pages 3152-3154, see entire document.	1-13

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-13, drawn to an isolated nucleic acid molecule encoding a polypeptide with the amino sequence set forth in SEQ ID NO:5 OR 7, or SEQ ID NO:6 or 8, the encoded protein, a recombinant vector, a host cell and a method of producing the encoded polypeptide.

Group II, claim 14, drawn to an isolated antibody that selectively binds to the GRAIL protein.

Group III, claim 15, drawn to a method for screening active agents that modulate GRAIL function.

Group IV, claim 16, drawn to a method of characterizing the expression of sequences associated with anergy induction or maintenance in T cells.

Group V, claims 17-19, drawn to a method of decreasing the responsiveness of a T cell population.

CHAPTER I
PCT TELEPHONE MEMORANDUM
FOR
LACK OF UNITY OF INVENTION



PCT No.: PCT/US01/15385

Examiner: FOZIA HAMUD

Attorney spoken to: PAMELA SHERWOOD

Date of call: 16 JULY 2001

- ☐ Amount of payment approved:
- ☐ Deposit account number to be charged:
- ☐ Attorney elected to pay for ALL additional inventions
- ☐ Attorney elected to pay only for the additional inventions covered by
 - ☐ Group(s):
 - encompassing --
 - ☐ Claim(s):
- ☒ Attorney elected **NOT** to pay for any additional inventions, therefore, only the first claimed invention (Group I) covered by Claim(s) 1-13, SEQ ID NOS:5-8 has been searched.
- ☒ Attorney was orally advised that there is no right to protest for any group not paid for.
- ☒ Attorney was orally advised that any protest must be filed no later than 15 days from the mailing of the Search Report (PCT/ISA/210).

Time Limit For Filing A Protest

Applicant is hereby given 15 days from the mailing date of this Search Report in which to file a protest of the holding of lack of unity of invention. In accordance with PCT Rule 40.2, applicant may protest the holding of lack of unity only with respect to the group(s) paid for.

Detailed Reasons For Holding Lack of Unity Of Invention:
(Continued on a separate sheet)

Note: A copy of this form must be attached to the Search Report.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 14-19

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination (*specify*).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _ are so unclear that no meaningful opinion could be formed (*specify*).

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 14-19.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

ATTACHMENT TO CHAPTER I PCT TELEPHONE MEMORANDUM
FOR
LACK OF UNITY OF INVENTION

Detailed Reasons For Holding Lack Of Unity Of Invention:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-13, drawn to an isolated nucleic acid molecule encoding a polypeptide with the amino sequence set forth in SEQ ID NO:5 OR 7, or SEQ ID NO:6 or 8, the encoded protein, a recombinant vector, a host cell and a method of producing the encoded polypeptide.

Group II, claim 14, drawn to an isolated antibody that selectively binds to the GRAIL protein.

Group III, claim 15, drawn to a method for screening active agents that modulate GRAIL function.

Group IV, claim 16, drawn to a method of characterizing the expression of sequences associated with anergy induction or maintenance in T cells.

Group V, claims 17-19, drawn to a method of decreasing the responsiveness of a T cell population. The inventions listed as Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Pursuant to 37 C.F.R § 1.475 (d), the ISA/US considers that where

multiple products and processes are claimed, the main invention

shall consist of the first invention of the category first

mentioned in the claims and the first recited invention of each

of the other categories related thereto. Accordingly, the main

invention (Group I) comprises the first-recited product, the

isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO:5 or 7 and the nucleic acid molecule encoding it, a vector comprising said nucleic acid molecule, a host cell and a method of producing the encoded polypeptide. Further pursuant to 37 C.F.R § 1.475 (d), the ISA/US

considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within

the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

To: PAMELA J. SHERWOOD
BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD ROAD
SUITE 200
MENLO PARK CA 94025

Date of Mailing
(day/month/year) **15 APR 2002**

Applicant's or agent's file reference
STAN-177WO

REPLY DUE
within TWO months
from the above date of mailing

International application No. PCT/US01/15385	International filing date (day/month/year) 11 MAY 2001	Priority date (day/month/year) 11 MAY 2000
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International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

Applicant
THE BOARD OF TRUSTEES OF THE LELAND STANDFORD JUNIOR UNIVERSITY

BEST AVAILABLE COPY

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV ☐ Unity of invention
- V ☒ Statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; and explanations supporting such statement
- VI ☐ Documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

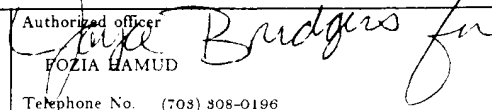
How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 11 SEPTEMBER 2002

DOCKETED
15 APR 2002
BY 10011000

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer  FOZIA HAMUD Telephone No. (703) 308-0196
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I. Basis of the opinion**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed
- ☒ the description:
pages 1-28, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the claims:
pages 29-30, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the drawings:
pages 1-10, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the sequence listing part of the description:
pages 1-8, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☒ contained in the international application in printed form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages None
- ☒ the claims, Nos. None
- ☒ the drawings, sheets/fig None

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims 2, 12	YES
	Claims 1, 3-11, 13	NO
Inventive Step (IS)	Claims 2, 12	YES
	Claims 1, 3-11, 13	NO
Industrial Applicability (IA)	Claims 1-13	YES
	Claims none	NO

2. citations and explanations

claims 1, 7-11 lack novelty under PCT Article 33(2) as being anticipated by US 5,534,631 [Li et al].

Li et al teach an isolated nucleic acid molecule that encodes an interleukin binding factor (ILF), an expression vector comprising said nucleic acid, a host cell transfected with said expression vector and a method of producing the encoded protein. The ILF disclosed by Li et al activates IL-2 gene expression in T-lymphocytes, (see abstract, column 4, lines 30-40 and claim 4). Instant claim 1 is drawn to an isolated nucleic acid that encodes a Grail protein and instant claims 7-10 are drawn to an expression cassette comprising nucleic acid encoding GRAIL, a host cell and a method of producing GRAIL protein. The disclosure describes GRAIL protein as being able to attenuate IL-2 transcription in T cells, (see page 2, lines 35-36). Therefore, since Applicants do not recite specific describing features for the claimed GRAIL gene, and since GRAIL is not an art recognizable term, the claim is interpreted as being drawn to an isolated nucleic acid encoding a protein that attenuates IL-2 transcription in T cells. Thus, Li et al reference anticipates instant claims 1, 7-11, because the ILF protein they disclose activates IL-2 expression.

Claims 3-6 lack novelty under PCT Article 33(2) as being anticipated by Marra et al. Marra et al teach a 769 cDNA clone. The cDNA disclosed by Marra et al shares 98.2% homology to the claimed nucleic acid sequence comprising the nucleotide sequence set forth in SEQ ID NO:5, from nucleotide 1243 to nucleotide 2012. Therefore, the cDNA disclosed by Marra et al meets the fragment limitations recited in instant claims 3-5. Also the cDNA disclosed by Marra et al would be expected to hybridize instant SEQ ID NO:5 under stringent conditions, thus anticipating instant claim 5.

Claim 13 lacks novelty under PCT Article 33(2) as being anticipated by Wilson et al. Wilson et al disclose an isolated protein that comprises 473 amino acid residues. The protein (Continued on Supplemental Sheet.)

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C12N 15/12, 5/10; C12P 21/02; C07K 14/47 and US Cl.: 435/69.1, 71.1, 320.1, 471, 252.3; 536/23.5; 530/350

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

disclosed by Wilson et al is purified and has at least 12 consecutive amino acids of instant SEQ ID NO:6. Therefore, the Wilson et al reference anticipates instant claim 13.

Claims 2 and 12 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest an isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:5 or 7 or a purified polypeptide encoded by said nucleic acid molecule.

----- NEW CITATIONS -----

US 5,534,631 A (LI et al) 09 June 1996, see entire document, especially column 4, lines 30-40 and claim 4).